Antiarrhythmic Drugs

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Vaughan Williams (1970) Classification of AAD

- **Class I:** Sodium channel blockers
- **Class II:** Beta-blockers
- **Class III:** Potassium channel blockers
- **Class IV:** Calcium channel blockers
- Sicilian Gambit Classification (1991)

Class I Antiarrhythmic Drugs

- **Class I:** block fast sodium channel
- **Class IA:** reduce V_{max} and prolong APD
  quinidine, procainamide, disopyramide
- **Class IB:** shorten APD
  lidocaine, mexiletine, phenytoin
- **Class IC:** reduce V_{max} and ↓ conduction
  propafenone, flecainide, moricizine

Quinidine (Class IA)

- **History:**

  * the oldest antiarrhythmic drugs
  * (1749) cinchona alkaloids
  * (1848) antimalarial agent, had antiarrhythmic action
  * (1918) routine use for atrial fibrillation

- **Mechanisms:**

  * blocks sodium and potassium channels
    affects depolarization and repolarization
  * blocks a1-& a2-adrenergic receptors,
    and muscarinic receptor

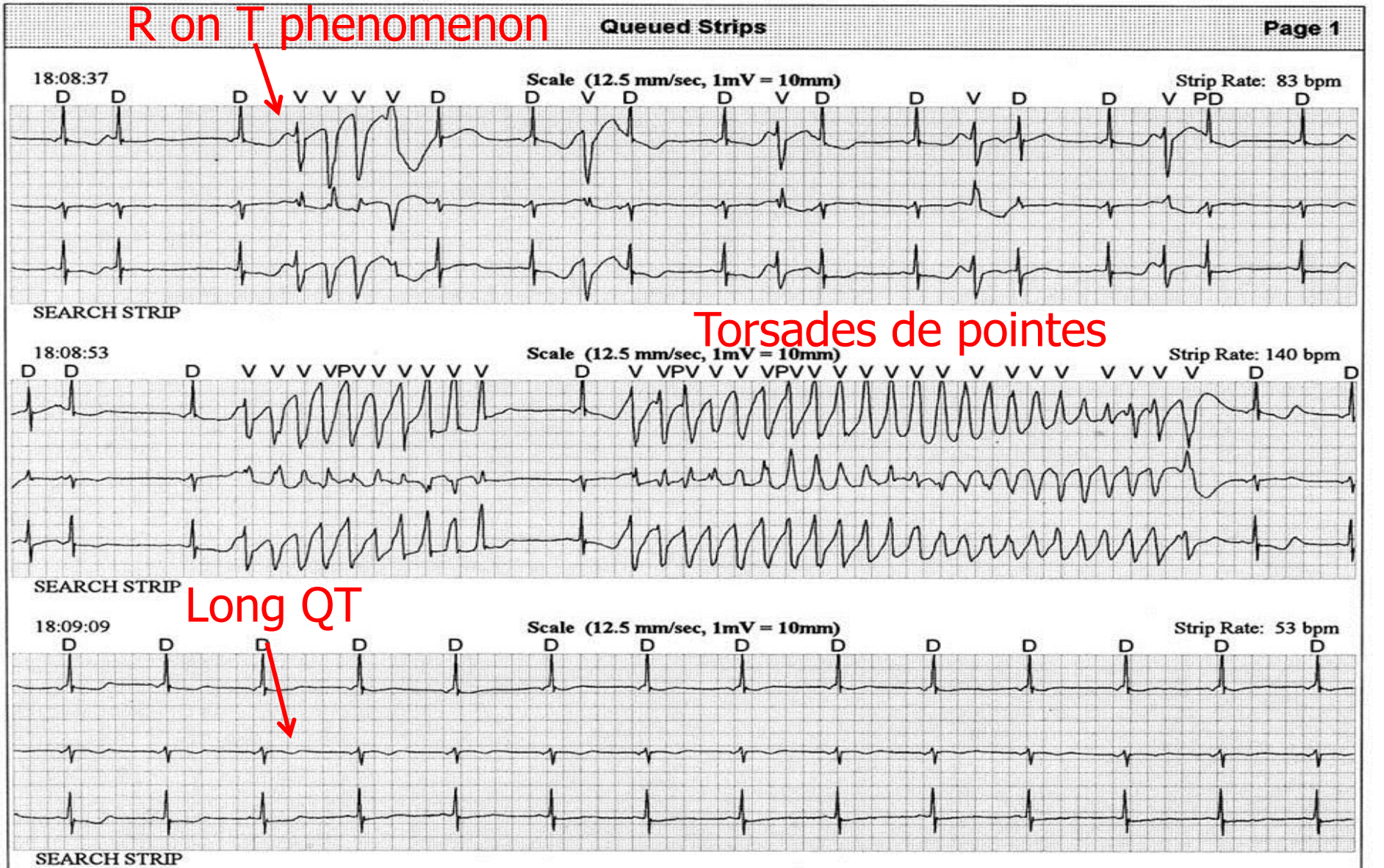
Quinidine (Class IA)

- **Hemodynamics:**
  - * orthostatic hypotension & reflex tachycardia
  - * enhance AV node conduction
- **Effects:**
  - * suppressed automaticity and DADs, created EADs, prolonged QTc
- **Side effects:**
  - * GI side effects : abdominal pain & diarrhea
  - * Cinchonism : decreased hearing, tinnitus, and blurred vision
  - * Thrombocytopenia, lupus syndrome

Quinidine (Class IA)

- **Proarrhythmia:**
  - * **Quinidine syncope:** VT, VF or TdP (torsades de pointes), 0.5% to 4.4%, not dose-related
  - * Discontinued drug when **QTc > 500 ms**
  - * **Avoid hypo K^{+}, Ca^{++}, Mg^{++}**
- **Efficacy:**
  - * Effective against supraventricular or ventricular arrhythmias, especially in conversion of AF to NSR.
- **Dosing:**
  - * oral 300 to 600 mg q6h
  - * IV 10 mg/Kg for > 20 mins

LQTS with TdP



Lidocaine (Class IB)

* Local anesthetic in 1946

  Antiarrhythmic drug in 1950
* IV form T1/2 = 8~10 minutes

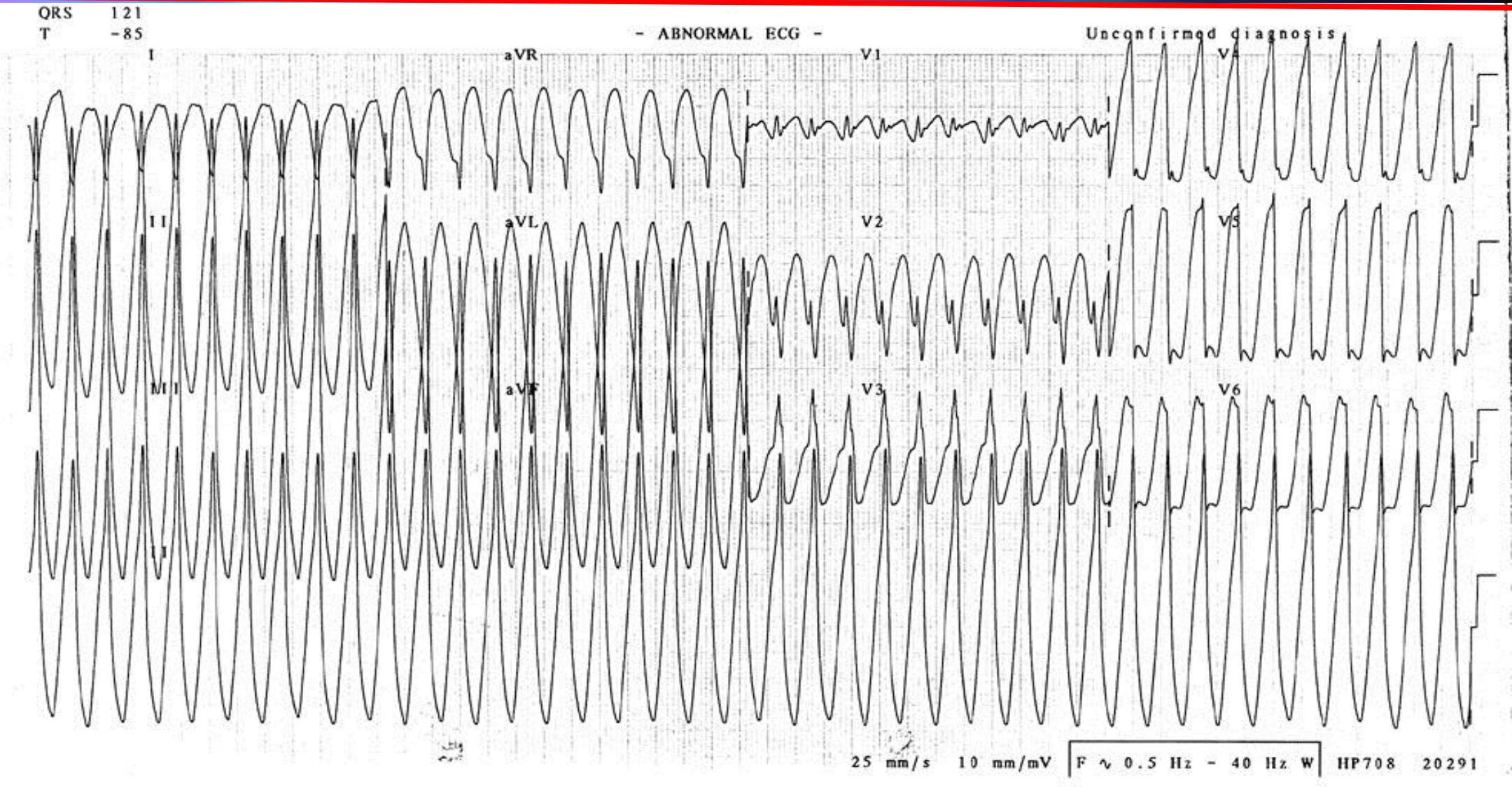
Mechanisms:

* Blocks I_{Na} current, predominant the inactivated state
* Suppresses normal or abnormal automaticity
* Suppresses the EADs and DADs
* Depresses excitability and conduction

Lidocaine (Class IB)

* CNS side effects: paresthesia, diplopia, slurred speech, altered consciousness, seizure, respiratory arrest, and coma.
* Proarrhythmia: rare
* Drug of first choice: acute treatment of hemodynamic stable monomorphic VT
* Loading dose: bolus of 1.5 mg/kg, three additional bolus (half of the initial dose), every 9 minutes

VT


QRS 121
T -85
- ABNORMAL ECG -
Unconfirmed diagnosis
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
25 mm/s 10 mm/mV
F ∿ 0.5 Hz - 40 Hz W
HP708 20291

Propafenone (Class IC)

* FDA approval in 1989.
* Not recommended use during pregnancy.

Mechanisms:

* Blocks I_{Na} current, use-dependent manner, both the activated and inactivated state
* Blocks I_K, L-type calcium channels (1/75 of verapamil)
* Nonselective β-adrenergic block
* Negative inotropic effects

Propafenone (Class IC)

Side effects:

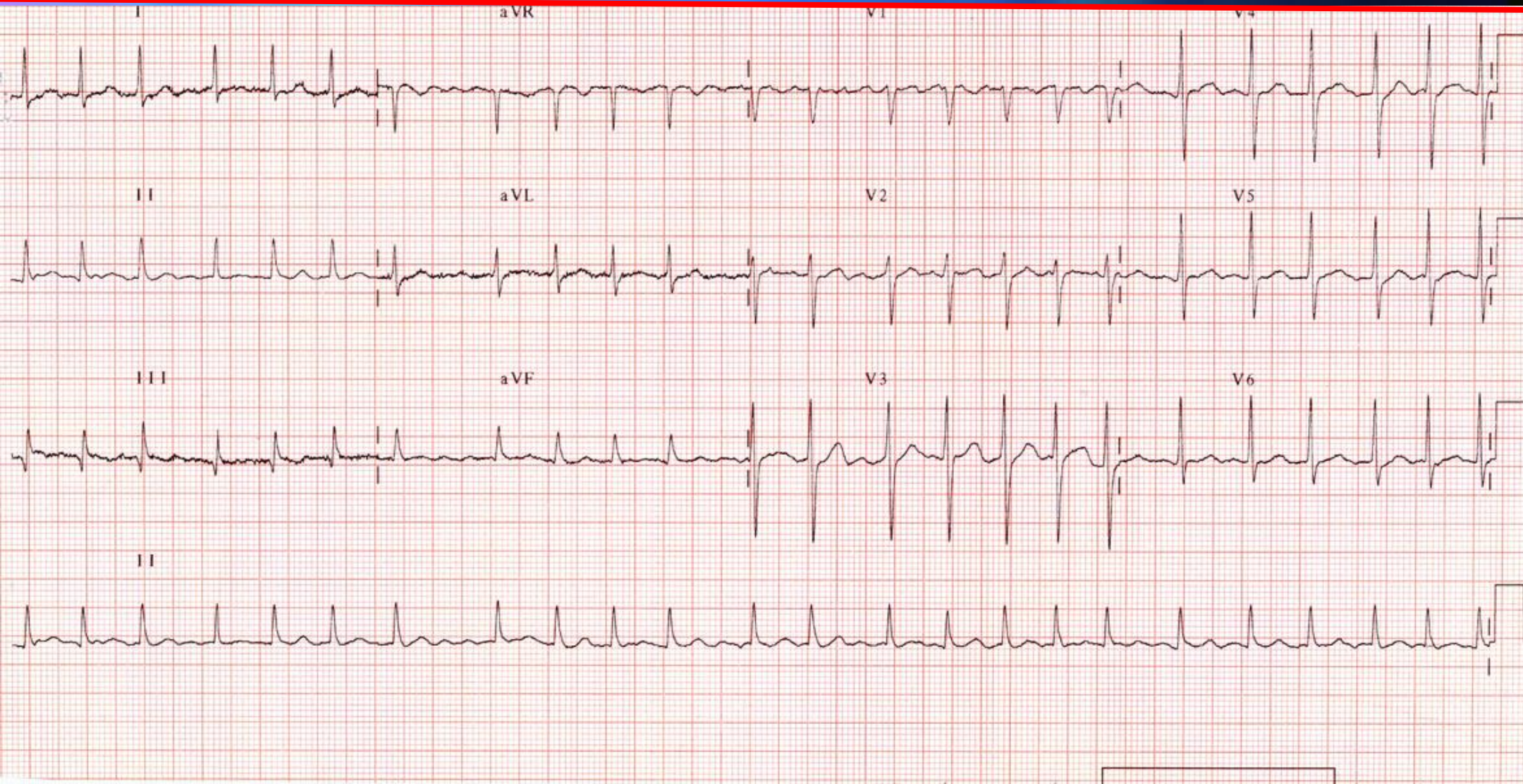
* Nausea, dizziness-most common side effects
* Blurred vision, paresthesias, increased liver function, exacerbation of asthma.
* Proarrhythmia: 5% (ventricular arrhythmia: polymorphic VT/VF; Inccessant VT, atrial flutter with 1:1 conduction)

Clinical use:

- Effective against a wide range of supraventricular and ventricular arrhythmias, especially in paroxysml AF

* Single PO loading dose (600 or 900 mg) : in converting recent-onset AF

Atrial Fibrillation



βeta-blockers (Class II)

Mechamismes: βeta-adrenergic receptors block

* Depresses the slope of phase 4 and suppress automaticity
* Prolongation of conduction in the atria and AV node
* Action potential duration & QT internal : controversial

Clinical effects:

* Modest effect in suppressing ventricular and supraventricular arrhythmias
* Elevation of ventricular fibrillation threshold

βeta-blockers on Ventricular arrhythmias

Non-sustained ventricular arrhythmias

* Produces a variable degree of premature ventricular contractions (PVCs) suppression
* First-line drug therapy for symptomatic ventricular arrhythmias

Sustained Monomorplic VT

* No direct effects on ischemic VT
* Effective in control of catecholamine-sensitive VT

Polymorphic VT/VF

* Adjuvant therapy for implantable cardioverter defibrillators (ICDs) to control VT/VF
* The cornerstone of therapy for congenital long QT syndrome : ↓ sympathetic activation

βeta-blockers on Supraventricular Tachyarrhythmias

Paroxysmal Supraventricular Tachycardia (PSVT)

* Acute termination of PSVT: 50%.
* Prevent recurrence of PSVT: efficacy unknown.

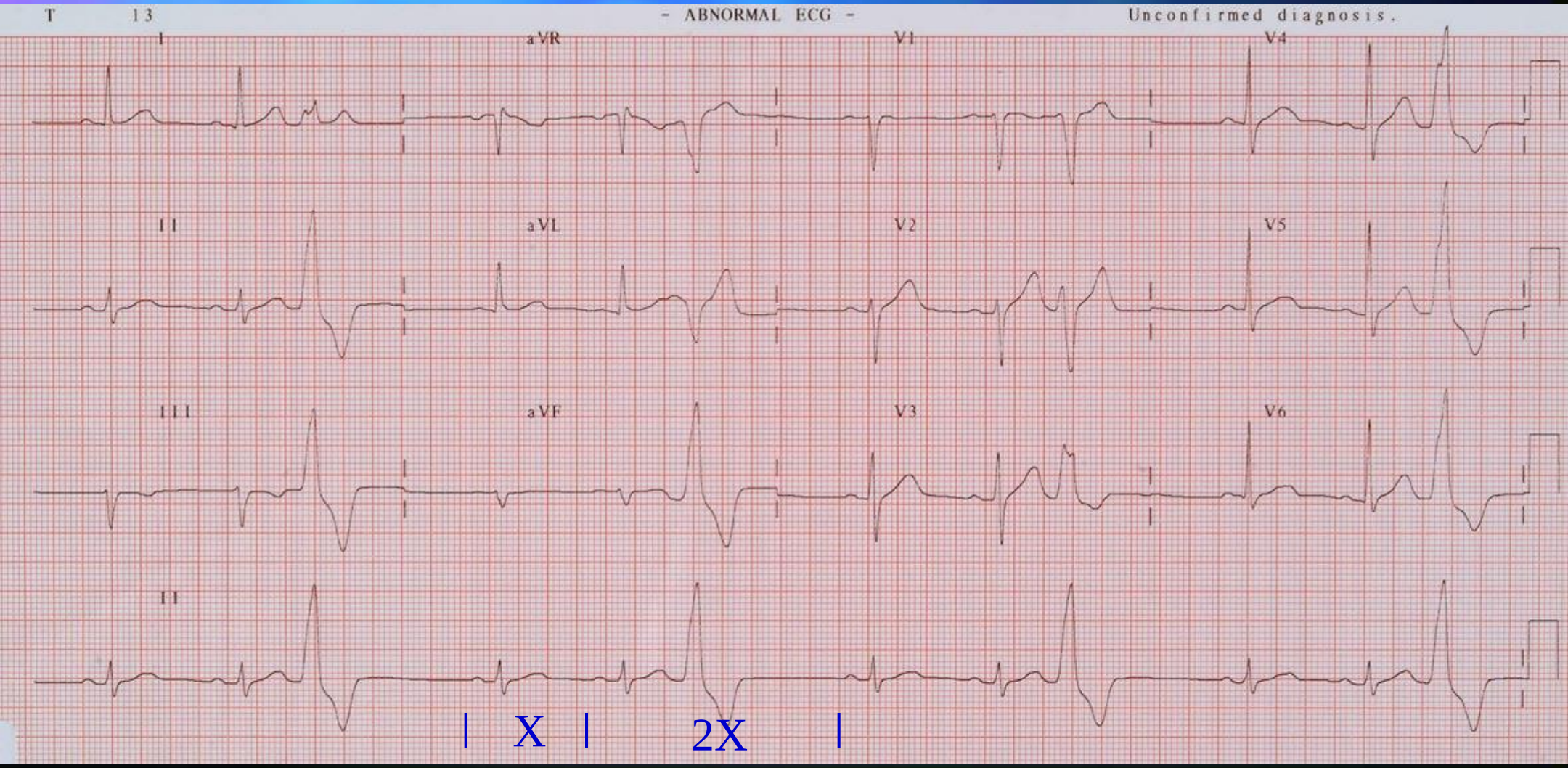
Ectopic atrial tachycardia (AT)

- Not uniformly effective in termination or suppression of AT.

Atrial flutter (AFL) and Atrial fibrillation (AF)

* No specific antifibrillatory properties for AF
* **Slowing** of AV conduction, reduce ventricular rate of AFL/AF.
* No significant effects on conversion of AFL and AF to SR.
* **Reduction in the incidence of AF** following cardiac surgery.

Trigeminal VPCs



Calcium Channel Blockers (Class IV)

* More than six classes of calcium channels, only two in the cardiovascular system: L-type and T-type calcium channels.
* L-type calcium channels are found in skeletal, cardiac and smooth muscle cells.
* T-type calcium channels: in the pacemaker cells and in Punkinje fibers, not in the ventricular myocytes.
* L-type CCBs: Verapamil, Diltiaiem and Nifedipine (No effects on cardiac arrhythmias).

  T-type CCBs: Miberfradil.
* Normal AV node: slow (calcium) channel dependent.
* Major effects of CCBs : in the AV node, no significant effects on atrial, ventricular or His-Purkinje fibers.

CCBs on Ventricalar Arrhythmias

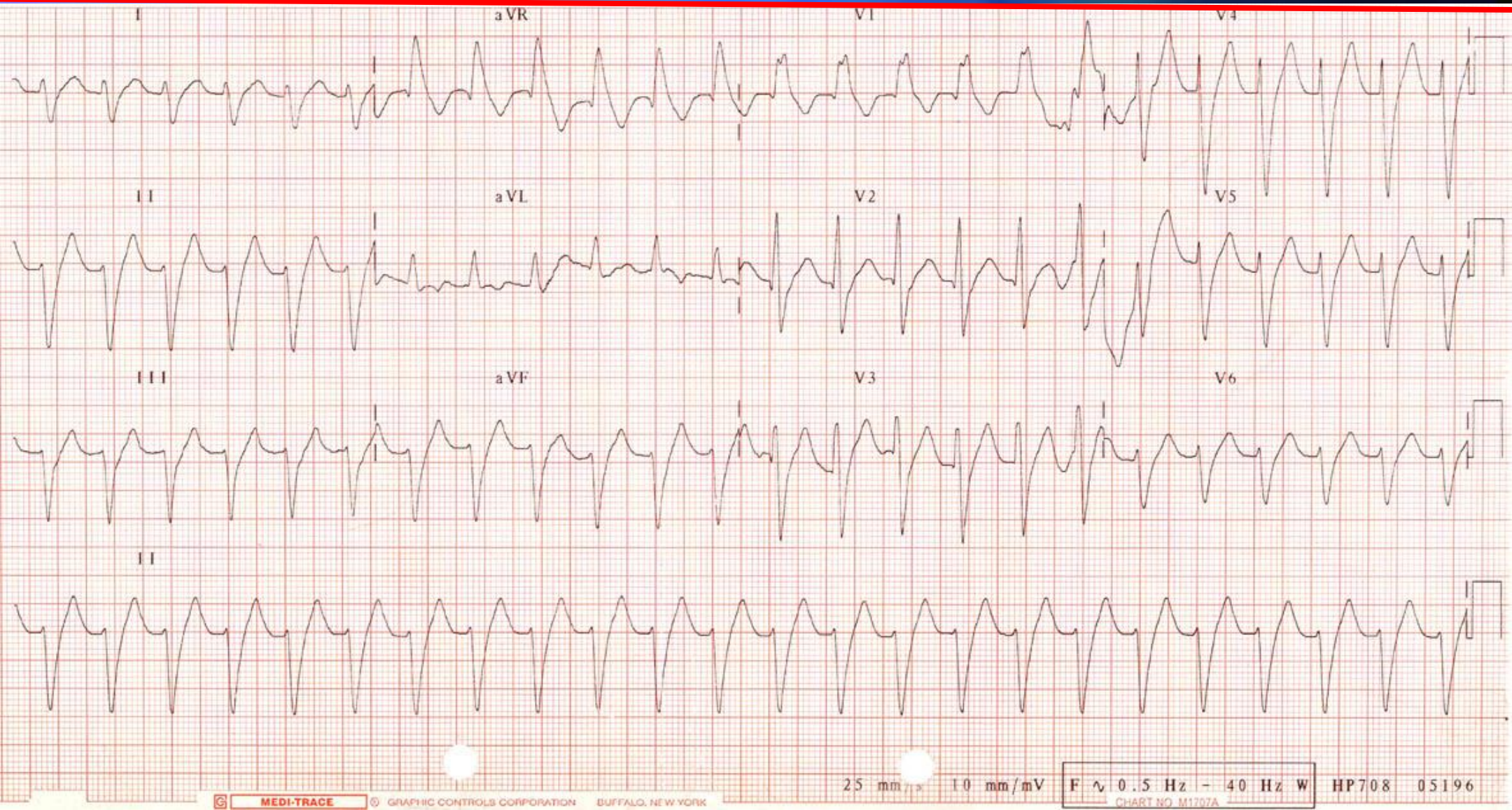
* No effect in suppression of PVCs
* Ischemic VT/VF: No clinical effects

VT in Patients with normal heart

* Exercise-triggered VT (EKG: LBBB, RVOT origin): Verapamil maybe effective
* Idiopathic LV-VT (EKG: RBBB+LAD)

-response to IV verapamil

Idiopathic LV-VT



CCBs on Supraventricular Tachycardias

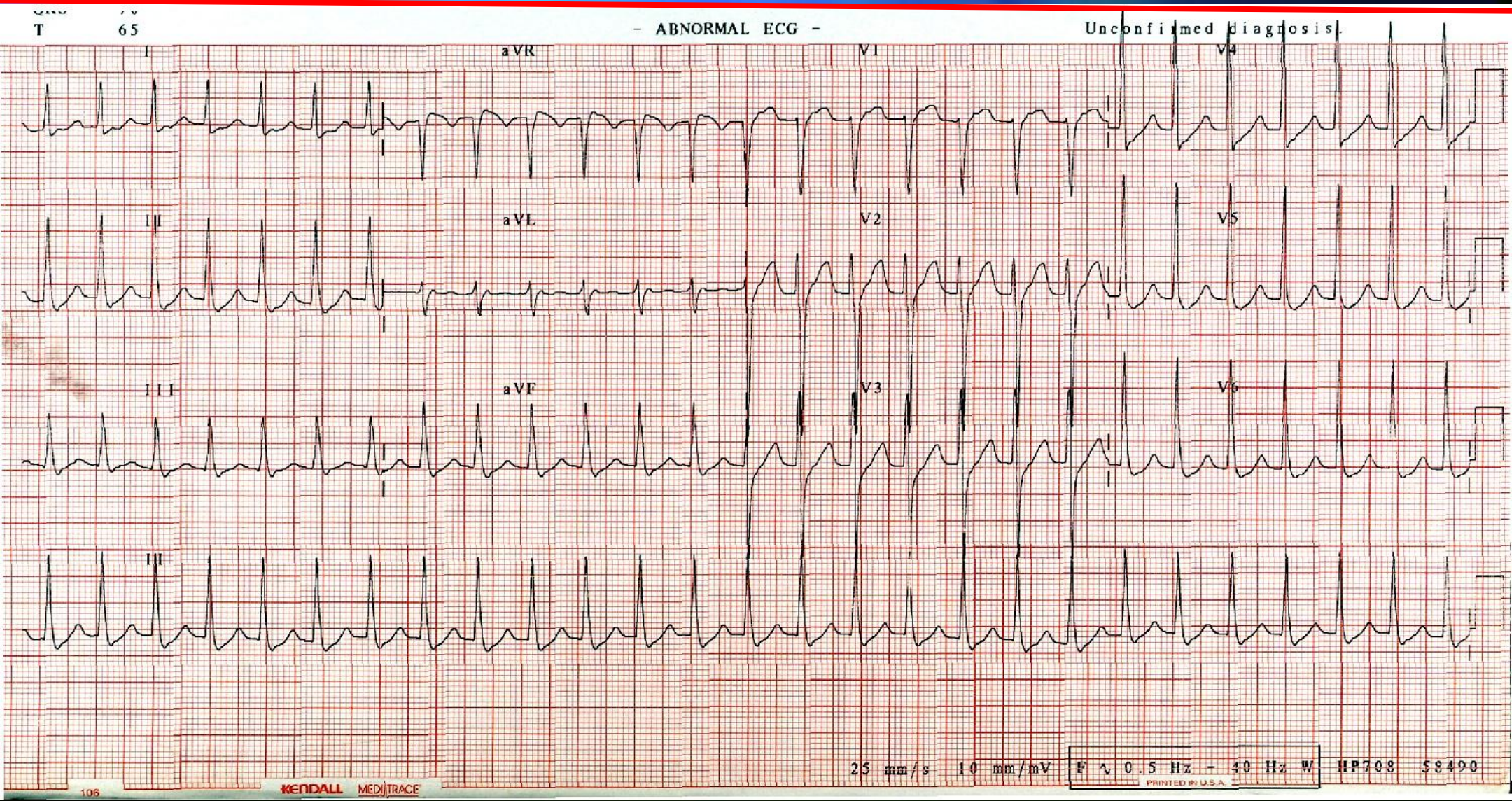
Acute termination of PSVT:

* **Beta-blocker: 40 ~ 50%**
* **Digoxin:45 ~ 55%**
* **Class I agents: 50 ~ 75%**
* **Class III agents: 65 ~ 85%**
* **Verapamil: 80 ~ 90% (10 mg slow infusion)**
* **Adenosie: around 90% (12 mg bolus)**

Drug of choice for PSVT: IV adenosine or verapamil

* **Prevent recurrence of PSVT: Limited**

AVNRT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CCBs on Supraventricular Tachycardias

Multifocal atrial tachycardia (MAT):

maybe effective in termination

Preexcitation syndrome: (WPW) syndrome

* Oral prophylaxis of orthodromic AVRT : not defined
* **Contraindications** in patients with AFL and AF complicating preexication: CCBs, B-blocker, digitalis, and adenosine

Atrial flutter and Atrial fibrillation:

* **slowing** the ventricular response of AFL or AF--IV or oral verapamil or diltiazem

Adenosine (I)

- An endogenous nucleoside--an important biochemical intermediate.
- A number of receptors subtypes: A1, A_{2A}, A_{2B}, A3.

Direct action:

* Activation of an outward potassium current (IK_{ADO}) in the atrium, sinoatrial (SA) and atrioventricular (AV) nodes.
* Inhibition of the pacemaker current (If) in SAN and AVN.
* Slight inhibition of a non-sustained basal inward calcium current (Ica) in atrial myocytes.

Indirect action:

- inhibition of intracellular cAMP generation.

Adenosine (II)

Clinical effects:

* **Half-life: 0.5 to 5 seconds**
* **Rapid IV bolus of adenosine resulted in**
  -- **a transient (< 10 seconds) sinus slowing with or without AV block, followed by a short (15-45 seconds) period of sinus tachycardia**
* **In the atria: shortens action potential duration and effective refractory period**
* **Dipyridamole: blocks cellular uptake of adenosine**
* **Methylxanthines: adenosine A1 & A2 antagonists**

Adenosine (III)

Paroxysmal Supraventricular Tachycardia:

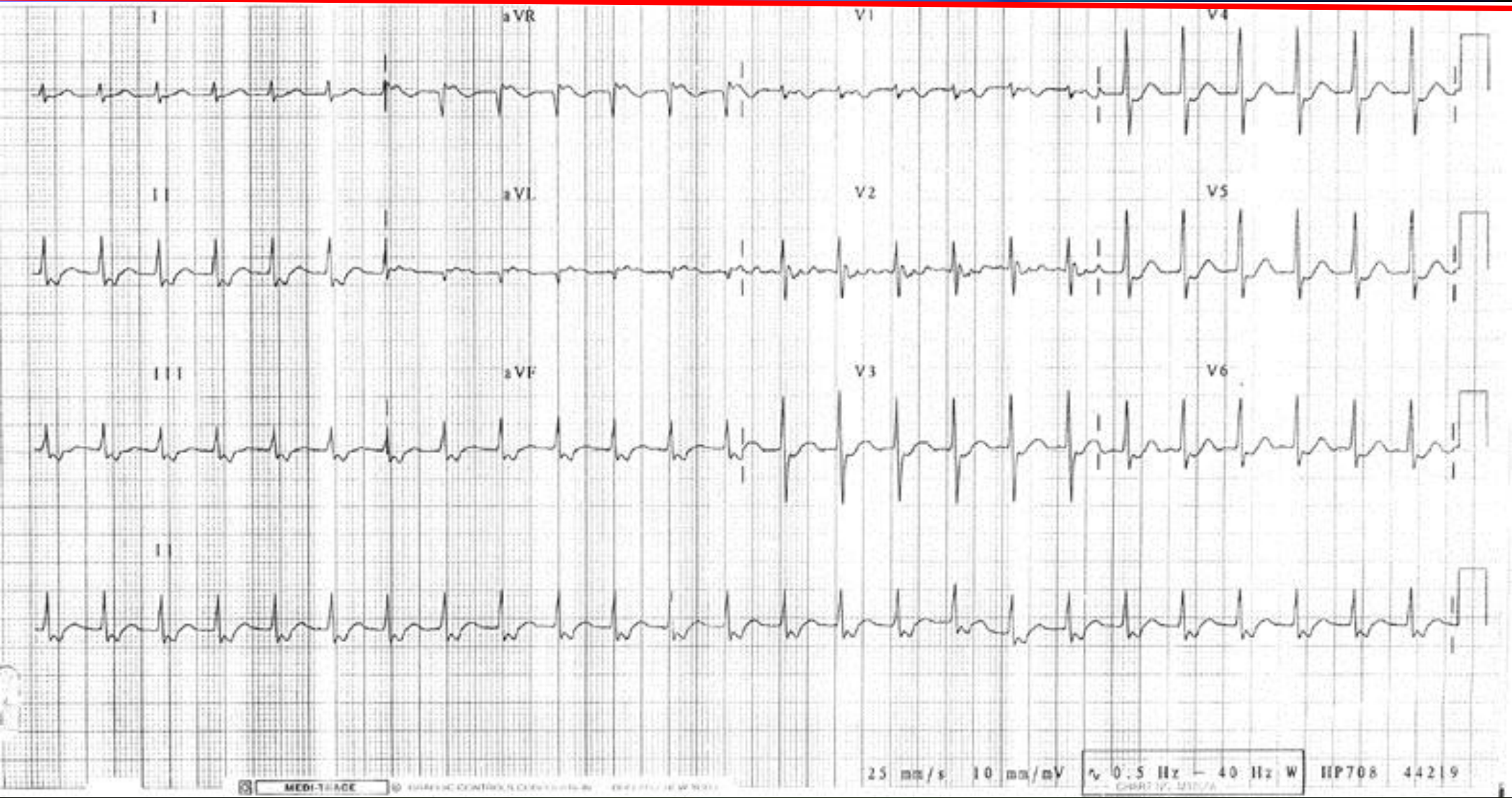
* Two common forms :AV nodal reentry or AV reentry tachycardia require intact AV nodal conduction
* First choice for terminating PSVT:

  IV adenosine or verapamil

Side effects:

* facial flushing, chest pain, and dyspnea
* Bronchospasm
* Proarrhythmia: frequent PACs or PVCs, AF & VF

Orthodromic AVRT



Adenosine (IV)

Atrial tachyarrhythmias:

* Atrial tachycardia : variable response, dependent on the mechanisms (reentry or triggered activity)
* AFL or AF : transient AV block (for diagnosis) with secondary acceleration of ventricular rate

Ventricular tachycardia:

* No direct effects on ventricular myocytes in human
* Inhibits catecholamine-stimulated calcium currents

  Inhibits EADs and DADs
* Effective in termination of RVOT-VT

Digitalis (I)

Mechanisms:

* directly inhibits sodium-potassium adenosine triphosphatase (Na-K ATPas)--> increases intracellular calcium concentration
* Major antiarrhythmic effects: mediated by central and peripheral actions to augment vagal tone
* At high level : increases sympathetic tone and automaticity, and DADs

Digitalis (II)

Clinical effects:

* In the AV node : slowing conduction and prolonged effective refractory period
* In the sinus node : minimally slowed the automaticity except in patients with SAN dysfunction
* In the atria : shortened refractory period and more rapid conduction
* Toxic level : increased automaticity in both supraventricular and ventricular tissues.

Digitalis (III)

Antiarrhythmic use:

* The major role : control of ventricular rate during atrial tachyarrhythmias
* New-onset of AF : effective control is delayed for at least 4 to 12 hours
* Chronic AF : the primary candidates for digoxin therapy, especially in patients with CHF

Side effects:

* anorexia, nausea & vomiting, headache, halo vision
* AV block, junction rhythm or bidirectional VT

Amiodarone (Class III)

- An initial antianginal agent
- Could serve as a textbook of how not to design a drug (Stanley Nattel)
- The most effective and safetest agent available for a variety of cardiac arrhythmias.

Mechanism:

* Reduce V_{max} and I_{Na} (class IB)
* Non-competitive adrenergic antagonism (class II)
* Prolongation of action potential duration (class III)
* Inhibiting I_{Kr}, I_{Ks}, and I_{K1}, and Blocks I_{Ca} (class IV)

Amiodarone (Class III)

Clinical use:

- Reduce the rate of sudden cardiac death post MI
- Increase the successful resuscitation rate of drug- resistant ventricular arrhythmias
- **Be safer and more effective** than other drugs in the maintenance of sinus rhythm in patients with AF.
- Reduce the incidence of postoperative AF

Amiodarone (Class III)

Side effects:

* Sinus bradycardia or slow ventricular response to AF
* Hypotension (IV form)
* Proarrhythmias: TdP rare, except hypokalemia
* Pulmonary fibrosis: maybe irreverible
* CNS side effects: anxiety, tremor, headache etc.
* Corneal microdepoit, photophobia, colored halo
* GI side effects: poor appetite, nausea, vomiting
* Cutaneous photosensitivity
* Thyroid function abnormalities

Atrial Flutter